

What is claimed is:

1. A method for inhibiting the expression of a gene in a cell comprising contacting the cell with an effective synergistic amount of an antisense oligonucleotide which inhibits expression of the gene, and an effective synergistic amount of a protein effector of a product of the gene.

2. A method for treating a disease responsive to inhibition of a gene in a mammal comprising administering to a mammal, including a human, which has at least one cell affected by the disease present in its body, a therapeutically effective synergistic amount of an antisense oligonucleotide which inhibits expression of the gene, and a therapeutically effective synergistic amount of a protein effector of a product of the gene.

3. A method for inhibiting tumor growth in a mammal comprising administering to a mammal, including a human, which has at least one neoplastic cell present in its body, a therapeutically effective synergistic amount of an antisense oligonucleotide which inhibits expression of a gene involved in tumorigenesis, and a therapeutically effective synergistic amount of a protein effector of a product of the gene.

4. The method of claim 1, 2, or 3, wherein the antisense oligonucleotide is in operable association with a protein effector.

5. The method of claim 1, 2, or 3, wherein the gene encodes a DNA methyltransferase.

6. The method of claim 5, wherein the protein effector is selected from the group consisting of 5-aza-cytidine, 5-aza-2'-deoxycytidine, 5-fluoro-2'-deoxycytidine and 5,6-dihydro-5-azacytidine.

7. The method of claim 1, 2, or 3, wherein the gene encodes a histone deacetylase.

8. The method of claim 7, wherein the protein effector is selected from the group consisting of trichostatin A, depudecin, trapoxin, suberoylanilide hydroxamic acid, FR901228, MS-27-275, CI-994, and sodium butyrate.

9. The method of claim 1, 2, or 3, wherein the gene encodes a thymidylate synthase.

10. The method of claim 9, wherein the protein effector is selected from the group consisting of 5-fluorouracil, Tomudex, Raltitrexed, Zeneca ZD1694, Zeneca ZD9331, Thymitaq, AG331, Ly231514, and BW1843U89.

11. The method of claim 1, 2, or 3, wherein the antisense oligonucleotide
5 has at least one internucleotide linkage selected from the group consisting of phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleotide linkages.

10 12. The method of claim 1, 2, or 3, wherein the antisense oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region and an alkylphosphonate or alkylphosphonothioate region.

13. The method of claim 1, 2, or 3, wherein the antisense oligonucleotide
15 comprises a ribonucleotide or 2'-O-substituted ribonucleotide region and a deoxyribonucleotide region.

14. The method of claim 1, wherein said cell is contacted with an effective synergistic amount of at least one antisense oligonucleotide for an effective period of time.

20 15. The method of claim 2 or 3, wherein the mammal is administered a therapeutically effective synergistic amount of at least one antisense oligonucleotide for a therapeutically effective period of time.

16. The method of claim 1, wherein said cell is contacted with an effective synergistic amount of at least one protein effector for an effective period of time.

25 17. The method of claim 2 or 3, wherein the mammal is administered a therapeutically effective synergistic amount of at least one protein effector for a therapeutically effective period of time.

18. The method of claim 1, wherein each of the antisense oligonucleotide and the protein effector is admixed with a pharmaceutically acceptable carrier prior
30 to contacting the cell.

19. The method of claim 2 or 3, wherein each of the antisense oligonucleotide and the protein effector is admixed with a pharmaceutically acceptable carrier prior to administration to the mammal.

5 20. The method of claim 1, wherein the antisense oligonucleotide and the protein effector are mixed prior to contacting the cell.

21. The method of claim 2 or 3, wherein the antisense oligonucleotide and the protein effector are mixed prior to administration to the mammal.

22. The method of claim 1, wherein the cell is contacted separately with each of the antisense oligonucleotide and the protein effector.

10 23. The method of claim 22, wherein the cell is contacted with the antisense oligonucleotide prior to being contacted with the protein effector.

24. The method of claim 23, wherein the gene encodes a DNA methyltransferase and wherein the contacted cell is induced to undergo apoptosis or is arrested in the S phase of the cell cycle.

15 25. The method of claim 22, wherein the cell is contacted with the protein effector prior to being contacted with the antisense oligonucleotide.

26. The method of claim 25, wherein the gene encodes a DNA methyltransferase and wherein the contacted cell is arrested in the G₁ phase of the cell cycle.

20 27. The method of claim 2 or 3, wherein the antisense oligonucleotide and the protein effector are separately administered to the mammal.

28. The method of claim 27, wherein the antisense oligonucleotide is administered to the mammal prior to the administration of the protein effector.

25 29. The method of claim 28, wherein the gene encodes a DNA methyltransferase and wherein the cell in the mammal to which the antisense oligonucleotide is administered prior to the administration of the protein effector is induced to undergo apoptosis or is arrested in the S phase of the cell cycle.

30. The method of claim 27, wherein the protein effector is administered to the mammal prior to the administration of the antisense oligonucleotide.

31. The method of claim 30, wherein the gene encodes a DNA methyltransferase and wherein the cell in the mammal to which the protein effector is administered prior to the administration of the antisense oligonucleotide is arrested in the G₁ phase of the cell cycle.

5 32. The method of claim 1, wherein the gene encodes a DNA methyltransferase and wherein the cell comprises a gene whose expression has been inactivated by methylation.

33. The method of claim 32, wherein expression of the gene whose expression has been inactivated by methylation is reactivated in the contacted cell.

10 34. The method of claim 32, wherein the gene whose expression has been inactivated by methylation is the p16^{ink4} tumor suppressor gene.

35. The method of claim 2 or 3, wherein the gene encodes a DNA methyltransferase and wherein the cell comprises a gene whose expression has been inactivated by methylation.

15 36. The method of claim 35, wherein expression of the gene whose expression has been inactivated by methylation is reactivated in the mammal to which has been administered the therapeutically effective synergistic amount of an antisense oligonucleotide and the therapeutically effective synergistic amount of a protein effector.

20 37. The method of claim 35, wherein the gene whose expression has been inactivated by methylation is the p16^{ink4} tumor suppressor gene.

38. An inhibitor of a gene comprising an antisense oligonucleotide which inhibits expression the gene in operable association with a protein effector of a product of the gene.

25 39. The inhibitor of claim 38, wherein the antisense oligonucleotide is in operable association with two or more protein effectors.

40. The inhibitor of claim 38, wherein the gene encodes a DNA methyltransferase.

30 41. The inhibitor of claim 40, wherein the protein effector is selected from the group consisting of 5-aza-cytidine, 5-aza-2'-deoxycytidine, 5-fluoro-2'-deoxycytidine and 5,6-dihydro-5-azacytidine.

42. The inhibitor of claim 38, wherein the gene encodes a histone deacetylase.

43. The method of claim 42, wherein the protein effector is selected from the group consisting of trichostatin A, depudecin, trapoxin, suberoylanilide hydroxamic acid, FR901228, MS-27-275, CI-994, and sodium butyrate.

44. The inhibitor of claim 38, wherein the gene encodes a thymidylate synthase.

45. The inhibitor of claim 44, wherein the protein effector is selected from the group consisting of 5-fluorouracil, Tomudex, Raltitrexed, Zeneca ZD1694, Zeneca ZD9331, Thymitaq, AG331, Ly231514, and BW1843U89.

46. The inhibitor of claim 38, wherein the antisense oligonucleotide has at least one internucleotide linkage selected from the group consisting of phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleotide linkages.

47. The inhibitor of claim 38, wherein the antisense oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region and an alkylphosphonate or alkylphosphonothioate region.

48. The inhibitor of claim 38, wherein the antisense oligonucleotide comprises a ribonucleotide or 2'-O-substituted ribonucleotide region and a deoxyribonucleotide region.

49. A pharmaceutical composition comprising the inhibitor of claim 38.

50. The composition of claim 49 further comprising a pharmaceutically acceptable carrier.